D4 ~~26~~. (Amended) The variant of claim [23]~~28~~ wherein position 277 [numbered in accordance with the mature plasminogen activator] is [occupied] substituted by an amino acid other than lysine.

Please amend claim 28 as follows:

D5 28. (Amended) The variant of claim 16 that is rendered resistant to enzymatic cleavage [at the] by an amino acid substitution at position 275 or the 277 site or both.

Sub a'

Remarks

The foregoing amendments, which serve to better define the invention claimed in this application, are clearly supported by the specification and claims as originally filed, and do not raise any issues of new matter introduction.

Turning now to the Office Action, claims 1, 11-12, 15-17, 24-28, 30-31, 58-60, 62-65, and 67-73 are pending in this application. Claims 1, 30-32, 58, 60, 62-65, and 67-71 were allowed. Claims 11-12, 15-17, 24-28, 59, and 72-73 were rejected on various grounds.

I.

Rejection under 35 U.S.C. § 102 (f) or (g)

Claims 59, 72, and 73 were rejected as being directed to an invention that is "not patentably distinct from claims 12-17 of commonly assigned [application Serial No.] 07/841,698." According to the rejection, application 07/841,698 "would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102 (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made." Applicants were, therefore, requested to "either show that the conflicting inventions were commonly owned at the time the

84

invention in this application was made or to name the prior inventor of the conflicting subject matter."

Applicants respectfully traverse this rejection, as (1) the invention claimed in claims 59, 72 and 73 of the present application, and the invention defined in claims 12-17 of copending application Serial No. 07/841,698, which has been refiled as application Serial No. 08/168,060, and will hereinafter be referred to as the "'060 application", are patentably distinct; and further because (2) the '060 application is not available as prior art under 35 U.S.C. § 102 (f) or (g)/103.

(1) In the present application, claim 59 concerns a method of treating a vascular disease or condition by administering a composition comprising a therapeutically effective amount of a glycosylation variant of t-PA as defined in claim 1.

Claim 72 concerns a method of treating a vascular disease or condition with a composition comprising a therapeutically effective amount of a t-PA variant having an extra glycosylation site at amino acid position 103 due to the substitution of asparagine at that position (see claim 65) and additionally having the glycosylation signal removed at at least one of amino acid positions 117, 184, 218 and 448 (see claim 68).

Claim 73 concerns a method of treating a vascular disease or condition with a composition comprising a therapeutically effective amount of a t-PA variant having an extra glycosylation site at amino acid position 103 due to the substitution of asparagine at that position (see claim 65), having alanine substituted at each of amino acid positions 296-299 of the native human t-PA (see claim 67), and additionally having the glycosylation signal removed at at

D

least one of amino acid positions 117, 184, 218 and 448 (see claim 69).

As a results of the amino acid substitutions detailed above, the t-PA variants administered in accordance with claims 59, 72 and 73 of the present invention exhibit a slower clearance from the plasma than wild-type t-PA.

The surprising recognition underlying the invention claimed in the '060 application is that native t-PA and t-PA variants exhibit a significantly extended circulatory half-life (decreased plasma clearance rate) when administered as a large (typically about 1.5 - 2.5 mg/kg of body weight) initial bolus. Accordingly, claims 12-17 of the '060 application concern a method for reducing the plasma clearance of t-PA variants, similar to those disclosed in the present application, by administering such variants to a patient in need of thrombolytic therapy **in an initial bolus dose substantially saturating their clearance mechanism**. The reduced plasma clearance rate in this case is not due to amino acid alterations in the wild-type t-PA sequence, rather is achieved by the specific way of administration recited in the claims.

There is absolutely no disclosure, suggestion or hint in the present application that would make obvious the specific administration protocol claimed in the '060 application. As the invention claimed claims 12-17 of the '060 application is patentably distinct from the invention claimed in claims 59, 72 and 73 of the present application, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Would the two inventions not be patentably distinct, the rejection should still be withdrawn. Both the inventors in the present application and the inventor of the '060 application were

employees of Genentech, Inc. when the respective inventions were made, and were under obligation to assign the rights in and to these inventions to Genentech. As at the time the later invention was made both of the claimed inventions were subject to an obligation for assignment to Genentech, Inc., the applications are not citable against each other under 35 U.S.C. § 102 (f) or (g)/103 (37 C.F.R. § 1.78(c)). Subsequent to the filing of the respective application, the rights were indeed assigned. The Assignment in the present case has been recorded on 30 March 1990 under Reel/Frame 5277/0157, while the Assignment in the parent of the '060 application has been recorded on 26 February 1992 under Reel/Frame 6061/670.

II.

Obviousness-type Double Patenting Rejections

A. Claim 59 of the present application was provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 12-15 of application Serial No. 07/841,698, now abandoned in favor of continuing application Serial No. 08/168,060 ("the '060 application").

The rejection is respectfully traversed. Claim 59 of the present application concerns a method of treating a vascular disease or condition by administering a composition comprising a therapeutically effective amount of a glycosylation variant of t-PA as defined in claim 1. Claims 12-15 of the '060 application were discussed hereinabove. For reasons given in response to the previous rejection, the inventions claimed in claim 59 of the present application and in claims 12-15 of the '060 application are patentably distinct, and deserve separate patent protection. Therefore, the Examiner is respectfully requested to reconsider and withdraw this rejection.

B. Claims 72 and 73 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 12-17 of application Serial No. 07/841,698, now abandoned in favor of continuing application Serial No. 08/168,060 ("the '060 application"), in view of Larsen *et al.* (WO 87/04722).

The claims involved in this rejection have been discussed in Section I above. Larsen was cited for its teaching of the removal of a glycosylation site at amino acid positions 117-119, 184-186, 218-220 and/or 448-450. According to the rejection, it "would have been obvious to take the copending 07/841,698 variants and further modify them according to Larsen *et al.* (WO 87/04722) and then use them in method of treatment."

The rejection is respectfully traversed. As discussed in response to the rejection under 35 U.S.C. § 102 (f) or (g)/103 in Section I above, the invention claimed in the '060 application is based on the unexpected finding that the plasma half-life of t-PA can be significantly extended without alteration of its amino acid sequence, by choosing a specific mode of administration, namely the administration of a large initial bolus dose, which may optionally followed by the administration of further boluses and/or by continuous intravenous administration. Notwithstanding the fact that this protocol is particularly advantageous for the administration of t-PA variants which already exhibit extended plasma half-life as compared to wild-type t-PA due to specific mutations in their amino acid sequence, such as those disclosed in the present application, the idea of administering t-PA (whether native or variant) as disclosed in claimed in the '060 application is clearly distinct from the idea that makes the present invention patentable, i.e. that the addition of extra glycosylation to native t-PA in certain positions extends its plasma half-life.

In view of the foregoing arguments the reconsideration and withdrawal of this rejection are respectfully requested.

III.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 15, 17, and 28 were rejected under 35 U.S.C. § 112, first paragraph for the following reasons:

(1) Claim 15: The disclosure was accepted to be enabling to only to the deletion of amino acids 1-44 of the finger region. Without acquiescence in this position, claim 15 now recites the deletion of the 1-44 aa region, which should overcome this rejection.

(2) Claim 17: The disclosure was found to be enabling only to the removal of glycosylation at the 184 amino acid position via amino acid substitution. As claim 17 has been amended accordingly, this rejection is moot.

(3) Claim 28: The specification was found to provide sufficient enablement only to substitution at amino acid positions 275 and 277 to render them resistant to enzymatic cleavage. Applicants submit that claim 28 as currently amended is clearly enabled by the specification, therefore, this rejection should be withdrawn.

IV.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11-12, 16, and 24-27 were rejected under 35 U.S.C. § 112, second paragraph as "being indefinite".

Claim 11 was found indefinite in referring to amino acid position 50, for which there is no antecedent basis in claim 1.

Claim 11 as amended no longer recites position 50, therefore, this rejection is moot.

Claim 16 was rejected for the use of the language "comprising natural t-PA". As the language objected to no longer appears in claim 16, and the claim has been amended in line with the Examiner's suggestion, the withdrawal of the present rejection would be in order.

Claims 24 and 26 were rejected for being dependent on a cancelled claim, while the reason for the rejection of claims 25 and 27 is probably their dependence on rejected claims. The foregoing amendment is believed to overcome this rejection.

Applicants note the Examiner's analysis of the Gething reference (U.S. Patent No. 5,041,376), which has not been applied to the claims of the present application.

Applicants were requested to bring to the attention of the Examiner any co-pending applications "containing similar subject matter". As the Examiner is well aware, pending applications from the same lineage as the present case are Serial Nos. 08/036,014 and 08/060,290. Further applications that might possibly be considered as related, but clearly patentably distinct, are Serial Nos. 07/808,121; 08/088,451; 08/179,059 and 08/178,945 all concerning various fibrin-specific t-PA variants. It is emphasized that the term "similar subject matter" is rather vague and subject to interpretation. Accordingly, the present information should by no means be construed as a representation that the list provided is

complete, and that other applications that might possibly be viewed as "related" do not exist.

The present application is believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Respectfully submitted,

GENENTECH, INC.

Ginger R. Dreger
Registration No. 33,055

Dated: March 11, 1994
460 Point San Bruno Boulevard
So. San Francisco, CA 94080-4990
(415) 225-3216